10/049,868

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hans DECKMYN et al.	Confirmation No.:	2345
Serial No.:	10/049,868	Art Unit:	1644
Filed:	June 4, 2002	Examiner:	Maher M. Haddad
Customer No.:	21559		

Title: CELL LINES, LIGANDS AND ANTIBODY FRAGMENTS FOR USE IN PHARMACEUTICAL COMPOSITIONS FOR PREVENTING AND TREATING HAEMOSTASIS DISORDERS

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. DÉSIRÉ COLLEN

1. I am a Professor at the University of Leuven and an expert in the field of vascular biology. A copy of my curriculum vitae is attached.

2. I am the CEO and Chairman of ThromboGenics, the exclusive licensee of this application.

3. I have read U.S. Patent Application Serial No. 10/049,868 and the Office Action mailed September 13th, 2006.

4. I understand that the above-reference application claims "A pharmaceutical composition comprising a monovalent antibody fragment ... and a pharmaceutically acceptable carrier."

5. I also understand that the Examiner asserts that the Tandon et al. (Biochem J. 1991, 274:435-542; "Tandon") and Wicki et al., (Eur J. Biochem. 1985, 153(1):1-11; "Wicki") references describe buffers which are considered to be pharmaceutical acceptable carriers. Here the Examiner asserts:

> Tandon et al reference teaches anti-glycocalicin Fab fragments against GPIb in 40 µg/well (page 537 under Role of membrane glycoproteins in particular). Further, Tandon et al teach that the platelets that were added to the well were in buffer A in the adhesion assay (see page 536, under Microtitre adhesion assay in particular), wherein buffer A is 5.0 mM-Tris, 5.5 mM-glucose, 150 mM-NaCl, 2.0 mM-MgCl2 and 0.5% BSA, pH 7.4. Buffer A is considered to be a pharmaceutical acceptable carrier. It is noted that glycocalicin is a proteolytic product of GPIbα.
>
> Wicki et al teach treatment of washed platelets with Fab fragments of rabbit antibodies to the 45-kDa fragment of glycocalicin (a major proteolytic cleavage product of GPIb) did not activate platelets but inhibited aggregation of the platelets by von Willebrand factor and their activation by thrombin (see page 7, 1st col. 1st full ¶ and page 8, 2nd col., at the end of the 1st ¶ in particular). Further, Wicki et al teach that the platelets that platelets were washed with calcium-free Tyrode's buffer (see page 1, 2nd col. last ¶ in particular) which is considered to be a pharmaceutical acceptable carrier.

For the following reasons, Tandon and Wicki neither teach a pharmaceutical composition nor a pharmaceutically-acceptable carrier.

6. I first note that the patent application describes pharmaceutical compositions and pharmaceutical carriers as follows:

> Suitable pharmaceutical carriers for use in the pharmaceutical compositions of the invention are described for instance in Remington's Pharmaceutical Sciences 16th ed. (1980) and their formulation is well known to those skilled in the art. They include any

and all solvents, dispersion media, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), isotonic agents (such as sugars or sodium chloride) and the like. Additional ingredients may be included in order to control the duration of action of the monoclonal antibody or Fab fragment active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate and the like. The rate of drug release and duration of action may also be controlled by incorporating the monoclonal antibody active or Fab fragment ingredient into particles, e. g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polymethyl methacrylate and the other above- described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition comprising the active ingredient may require protective coatings. The pharmaceutical form suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and mixtures thereof.

7. Tandon and Wicki describe the use of the anti-GP1b Fabs in vitro, i.e. on isolated platelets or blood samples. The Tandon and Wicki compositions are not pharmaceutical compositions because each lacks the sterility which is inherently required for every pharmaceutical composition; in particular, compositions that include an antibody. Moreover, because Tandon and Wicki were investigating the role of GP1b in platelet function in vitro, the compositions used by Tandon and Wicki do not require that they are sterile. Tandon and Wicki therefore do not describe pharmaceutical compositions as presently claimed in this application.

8. A second reason for which I do not consider the Tandon and Wicki compositions described in the context of in vitro experiments as pharmaceutical compositions is the fact that the Tandon and Wicki compositions are neither selected in view of tolerance by the patient nor based on the desired activity of the GP1b antibody fragment. Indeed, antibody fragments are generally provided in pharmaceutical compositions either freeze-dried or in saline, or in another physiologically neutral solution. The inclusion of buffers typically used in *in vitro* experiments renders such compositions unsuitable as pharmaceutical compositions.

9. I also note that Tandon et al. describe the use of a Buffer A. Buffer A includes 50mM Tris and 0.5%BSA. Tris (or Trishydroxymethylaminomethane) is an irritating product and is generally used for its strong buffering capacity, which can be relevant when working with different reagents in small volumes. Tris will however not be included in a pharmaceutical composition comprising antibody fragments, in view of its toxicity and the fact that antibodies either in the composition or upon administration to the patient remain under physiological conditions, such that there is no need for a strong buffering reagent. BSA (bovine serum albumin) is generally used in in vitro assays to avoid non-specific protein interaction. Platelets isolated from their natural environment (blood) are contacted with a BSA-containing buffer to avoid non-specific interaction of any peptide or protein with the platelets. There is however no reason to include BSA in a pharmaceutical composition that includes antibody fragments. Indeed, upon administration of the antibodies, the numerous proteins present in the body (including albumin) will ensure that non-specific interactions are avoided. Furthermore, in view of the very strict regulation on the inclusion of bovine

products in pharmaceutical compositions, the presence of bovine serum albumin in a composition comprising antibody fragments would make it unsuitable as a pharmaceutical composition.

10. The Tandon and Wicki compositions also do not contain a sufficient amount of monovalent antibody to bring about a therapeutic effect, and therefore the compositions are not pharmaceutical compositions.

11. Accordingly, for the reasons provided above, I disagree with the Examiner's position that the compositions mentioned in the in vitro studies of Tandon and Wicki are considered as pharmaceutical compositions. Although these compositions include monovalent antibodies directed against GP1b, Tandon and Wicki's compositions are plainly not pharmaceutical compositions.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 21 FEB 07

Dr. Désiré Collen

Désiré COLLEN

Curriculum vitae, February 7, 2007

Personal data

Gender:	male
Place and date of birth:	Sint Truiden, Belgium, June 21, 1943
Married to:	Reniers Louisa, July 14, 1966
Children:	An, born February 2, 1968
	Peter, born May 10, 1971
	Christine, born November 14, 1972
Address:	Schoonzichtlaan 20, B-3020 Herent, Belgium
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	B-3000 Leuven, Belgium
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Education

1968:	Doctor in Medicine (MD), KU Leuven, Belgium
1969:	Licentiaat (MSc) in Medical Sciences, KU Leuven, Belgium
1974:	PhD in Chemistry, KU Leuven, Belgium
1974:	Geaggregeerde "Higher Education in Medicine", KU Leuven, Belgium

Residencies and Research Fellowships

1968-1971:	Resident Internal Medicine, University Hospitals KU Leuven, Belgium
1971-1972:	Associate Research Scientist, New York University Medical Center, New York, N.Y.
1972-1973:	NATO Research Fellow, Karolinska Institutet, Stockholm, Sweden

Academic Appointments within the University of Leuven

1973-1976:	Aangesteld Navorser NFWO
1975-1976:	Extraordinary ("Buitengewoon") docent, Faculty of Medicine, KU Leuven
1976-1981:	Docent, Faculty of Medicine, KU Leuven, Belgium
1981-1998:	Professor, ("Gewoon hoogleraar") Faculty of Medicine, KU Leuven, Belgium
1990- :	Director of the Center for Molecular and Vascular Biology (previously Center for Thrombosis and Vascular Research) Faculty of Medicine, KU Leuven, Belgium
1998-2002:	Extraordinary Professor ("Buitengewoon hoogleraar"), Faculty of Medicine, KU Leuven, Belgium
2002-:	Professor, ("Gewoon hoogleraar") Faculty of Medicine, KU Leuven, Belgium

Academic Appointments outside the University of Leuven

1984- :	Professor of Biochemistry and Medicine, University of Vermont College of Medicine, Burlington, VT, USA
1986-1989:	Visiting Professor, Faculty of Medicine and Pharmacy, Free University Brussels, Belgium
1987-1994:	Visiting Professor of Medicine, Harvard Medical School, Boston, MA, USA
1994- :	Director of the Center for Transgene Technology and Gene Therapy Vlaams Interuniversitair Instituut voor Biotechnology Leuven, Belgium

Appointments in University Hospitals

1975-1976:	Consultant (Consulent), University Hospitals, KU Leuven, Belgium
1976-1998:	Adjunct Head of Clinic, University Hospitals, KU Leuven, Belgium
1987- :	Consultant in Medicine, Massachusetts General Hospital, Boston, MA, USA
1998- :	Consultant (Consulent), University Hospitals, KU Leuven, Belgium
1999-2002:	Visiting Professor in the Division of Surgery and Anaesthesia, Guy's King's and St. Thomas' School of Medicine, London, UK

Other Activities

1976-2001:	Division Head, Protein Research Division, Leuven Research and Development VZW, KU Leuven, Belgium
1988- :	Statutory Chairman of the D. Collen Research Foundation V.Z.W.
1991- :	Chairman of the Board of Thromb-X NV (Spin-off company of Leuven Research and Development, KU Leuven, Belgium)
1998- :	Chief Executive Officer and Chairman of ThromboGenics, Ltd., Ireland
2006- :	Chief Executive Officer, ThromboGenics, Ltd., Ireland
2006- :	Chief Executive Officer, ThromboGenics, NV, Belgium

Awards and Honors

1984:	Francqui Prize (University Foundation), Belgium
1985:	Member of the Royal Academy of Medicine of Belgium
1986:	Prix Louis Jeantet de Médecine (Fondation L. Jeantet), Geneva, Switzerland
1988:	Doctor honoris causa, Erasmus University, Rotterdam, the Netherlands
1990:	Five-yearly Prize of Fundamental Medical Sciences of the Belgian Government (Royal Academy of Medicine of Belgium)
1994:	Bristol-Myers-Squibb Award for Cardiovascular Research, New York, N.Y. (jointly with M. Verstraete)
1994:	Doctor honoris causa, Free University of Brussels (VUB), Brussels, Belgium
1995:	Doctor honoris causa, University of Notre Dame, Notre Dame, IN
1999:	Doctor honoris causa, Université de la Méditerranée, Marseille, France
2005:	Health Prize of the Interbrew-Baillet Latour Fund, Belgium (jointly with P. Carmeliet)
2006:	Elected member of the European Molecular Biology Organization (EMBO)
2007:	2007 Harvard Leadership Prize by the Harvard Club of Belgium

Research Areas

Molecular biology and pathophysiology of haemostasis and thrombosis
Development of new thrombolytic and antithrombotic agents
Pathogenesis and treatment of atherosclerosis
Transgenesis, gene targeting and gene transfer studies of the cardiovascular system

Research Output

The scientific output of D. Collen between 1968 and 2006 consists of approximately 645 research papers (in peer-reviewed international journals), 170 survey articles and 28 issued US patents (several with EPO and WO equivalents). He ranked among the 100 most cited scientific authors of the 1980's (Current Contents August 31, 1992, p3) and is listed with the highly cited authors of the 1980 and 1990's (http: //www.highlycited.com).

Relevant Links

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http://desirecollen.tripod.com
http://www.kuleuven.ac.be/mcm/
http://www.vib.be/Research/EN/Research+Departments/Department+of+Transgene+Technology+and+Gene+Therapy
http://www.isihighlycited.com/ (click: "Search by name", enter last name: "Collen")
http://www.thrombogenics.com
http://www.faseb.org/opa/break/ (click: "Clot Busters! – Discovery of Thrombolytic Therapy for Heart Attack and Stroke")